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Healthy preconception and early-pregnancy lifestyle and risk of preterm birth: a prospective cohort study

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ABSTRACT

Background: Preterm birth (PTB) remains a leading cause of neonatal mortality and long-term morbidity. Individual factors have been linked to PTB risk. The impact of a healthy lifestyle, with multiple modifiable prenatal factors, remains unknown.

Objectives: We aimed to examine the associations of preconceptional and early-pregnancy low-risk modifiable factors (individually and in combination) with PTB risk.

Methods: This prospective cohort study included 2449 women with singleton pregnancies in the Pregnancy Environment and Lifestyle Study. PTB was defined as ultrasound-confirmed obstetric estimate–based gestational age at delivery <37 wk. A set of low-risk modifiable factors were identified: healthy weight (prepregnancy BMI: 18.5–24.9 kg/m^2) based on clinical measurements and high-quality diet (Alternate Healthy Eating Index-Pregnancy score ≥75th percentile) and low-to-moderate stress during early pregnancy (Perceived Stress Scale score <75th percentile) assessed at gestational weeks 10–13. Poisson regression estimated adjusted relative risk (aRR) of PTB in association with individual and combined low-risk modifiable prenatal factors, adjusting for sociodemographic, clinical, and other prenatal factors.

Results: One hundred and sixty women (6.5%) delivered preterm. Risk of PTB was lower among women who had a healthy weight (aRR: 0.58; 95% CI: 0.39, 0.86), high-quality diet (aRR: 0.68; 95% CI: 0.39, 0.99), and low-to-moderate stress (aRR: 0.60; 95% CI: 0.41, 0.88). Women with 1, 2, or 3 low-risk modifiable prenatal factors compared with none had a 38% (aRR: 0.72; 95% CI: 0.45, 1.16), 51% (aRR: 0.49; 95% CI: 0.29, 0.84), or 70% (aRR: 0.30; 95% CI: 0.13, 0.70) lower PTB risk, respectively. Associations of having ≥1 low-risk factor with PTB risk were more pronounced for medically indicated than for spontaneous PTB and for late than for early or moderate PTB. Associations also varied by race or ethnicity, although with overlapping 95% CIs.

Conclusions: A healthy prenatal lifestyle with multiple low-risk modifiable factors was associated with lower risk of PTB. Our findings may inform multicomponent preconceptional or early-pregnancy prevention strategies to mitigate PTB risk. *Am J Clin Nutr* 2021;114:813–821.

Keywords: dietary quality, lifestyle, preconception, pregnancy, preterm birth, primary prevention, stress, weight

Introduction

Preterm birth (PTB), occurring before 37 weeks of gestation, is the second leading cause of neonatal mortality, accounting for 17% of infant deaths in the United States (1, 2). Whereas the

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Abbreviations used: AHEI-P, Alternate Healthy Eating Index for Pregnancy; aRR, adjusted relative risk; EHR, electronic health record; GWG, gestational weight gain; KPNC, Kaiser Permanente Northern California; PETALS, Pregnancy Environment and Lifestyle Study; PSS, Perceived Stress Scale; PTB, preterm birth.

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rate of PTB declined from 2007 to 2014 (3), it increased for the fifth consecutive year in 2019, complicating 10.2% of all births in the United States (4). Infants who survive PTB are predisposed to a myriad of short-term and long-term sequelae including adverse neurodevelopmental and cardiometabolic outcomes and premature mortality (5, 6), reinforcing the public health priority to prevent PTB. Most PTB prevention strategies to date have centered on tertiary intervention to prevent delivery or improve neonatal outcomes after the onset of the parturitional process, or secondary prevention to reduce existing risk among symptomatic women based on their obstetric history or present pregnancy risk factors (7, 8). The need for primary prevention among all pregnant women has become increasingly compelling given that more than half of PTBs occur in women without known risk factors (9).

The causes of PTB are multifactorial and include genetic traits, medical conditions, and sociodemographic and lifestyle factors (10, 11). Potentially modifiable factors, examined individually, that have been linked to risk of PTB include obesity (12–14), low diet quality or unhealthy dietary patterns (15–17), inadequate physical activity (18), stress (19), and smoking (20). Notably, multiple prenatal factors may synergistically or antagonistically compound the risk of PTB, making it difficult to disentangle the specific impact of individual risk factors. Indeed, given the multifactorial causes and heterogenic phenotypes of PTB, prevention strategies for PTB will necessarily have to address a wide range of factors through multicomponent lifestyle modification and multidisciplinary care. Further, preconceptional or early-pregnancy prevention strategies are particularly attractive because many mid-to-late pregnancy risk factors are difficult to modify successfully and in a timely way during pregnancy (8). However, the impact of an overall healthy prenatal lifestyle, consisting of multiple potentially modifiable preconceptional or early-pregnancy factors, remains understudied.

To address these important knowledge gaps, we aimed to prospectively examine the association of an overall healthy lifestyle, characterized by combinations of potentially modifiable preconceptional and early-pregnancy lifestyle factors, with risk of PTB in a racially and ethnically diverse cohort of women carrying singleton pregnancies. We also examined whether the associations may vary by clinical phenotypes of PTB and by self-identified race or ethnicity, given worrisome health disparities in PTB previously described in the literature.

Methods

Study population and design

This study is a secondary analysis of PETALS (Pregnancy Environment and Lifestyle Study), designed to examine associations of intrauterine environmental factors and risk of gestational diabetes. The study design has been described in detail elsewhere (21). This population was drawn from the membership of Kaiser Permanente Northern California (KPNC), an integrated health care delivery system serving 4.2 million members. The KPNC membership accounts for ~30% of the underlying population and its sociodemographic characteristics are representative of the population residing in the geographic areas served (22, 23). In brief, after weekly searches of the electronic health records (EHRs), all pregnant women aged 18–45 y, carrying singletons, and without recognized pre-existing diabetes, cancer, hepatitis C, or liver cirrhosis were invited to participate in the study before gestational week 11. Survey and anthropometric data were collected at a study clinic visit at gestational weeks 10–13; EHR data were abstracted from the year before the index pregnancy through delivery. The study has been approved by the human subjects committee of the Kaiser Foundation Research Institute. Written informed consent was obtained from all participants.

Among 2619 eligible pregnant women enrolled between October 2013 and December 2017, we excluded women who had pregnancy losses or stillbirths ($n = 39$) or moved out of the KPNC service region before delivering ($n = 7$). We further excluded women with missing data for the FFQ ($n = 97$) and implausible daily energy intake (<400 or >6000 kcal/d; $n = 27$), rendering an analytical sample of 2449 women (see the study flowchart in **Supplemental Figure 1**). The analytical sample did not vary from the 124 women with missing or implausible data by major participant characteristics.

Outcome ascertainment

Following the definition by the American College of Obstetricians and Gynecologists reVITALize Initiative, obstetric estimate of gestational age at delivery based on the best estimated delivery date was extracted from the EHR (24). Specifically, gestational age at delivery was based on the last menstrual period if confirmed by the early ultrasound, or early ultrasound dating if the 2 measures differed by >7 d. We previously validated obstetric estimate–based gestational age at delivery against early ultrasonographic examinations (gold standard) among both preterm and term infants (25). PTB was the primary outcome of this analysis and defined as a live birth before 37 weeks of gestation. Following a previous hierarchical algorithm (26, 27), we defined PTB clinical phenotypes as follows: *1*) spontaneous: if women presented in spontaneous labor even if they had other pregnancy indications and/or if women experienced premature rupture of the membranes; and *2*) indicated: if women required either an induction of labor and/or cesarean delivery. We also divided PTB into early (22–31 weeks of gestation), moderate (32–33 weeks of gestation), and late preterm (34–36 weeks of gestation) as done previously (15).

Assessment of potentially modifiable prenatal factors

Based on previous evidence on roles of potentially modifiable prenatal factors in PTB risk (12–20), we considered a priori the following modifiable preconceptional and early-pregnancy factors assessed at the study clinic visit at 10–13 weeks of gestation. Prepregnancy BMI was calculated as prepregnancy weight (kg) measured by clinical staff on average 11 wk before conception and abstracted from the EHR (97.5%) or by self-report (2.5%), divided by squared height (m^2) measured at gestational weeks 10–13. The Alternate Healthy Eating Index for Pregnancy (AHEI-P) was derived based on habitual dietary intake during the previous 3 mo ascertained via the Block FFQ administered at gestational weeks 10–13 (28), reflecting diet during preconception and early pregnancy. The nutrient and food group analysis database was developed from the USDA's Food and Nutrient Database for Dietary Studies version 5.0, the Food Pyramid Equivalents Database, and the Nutrient Database

for Standard Reference (29). The nutrient residual method was used to calculate energy-adjusted intakes of nutrients (30). The AHEI-P was adapted from the AHEI-2010 by Chiuve et al. (31) and an earlier pregnancy AHEI score by Rifas-Shiman et al. (32) as done previously (33). Specifically, the AHEI-P is a validated measure on a 130-point scale to assess overall dietary quality based on the 2010 USDA Dietary Guidelines for Americans with modification for pregnancy, consisting of 13 components (see the component list and distribution of each component in its original units in **Supplemental Table 1**). Stress during the last month was assessed by the 10-item Perceived Stress Scale (PSS) (34), which has been validated in various populations including pregnant women of diverse racial and ethnic backgrounds (35, 36). Physical activity during the year before the index pregnancy was assessed by the validated Pregnancy Physical Activity Questionnaire (37). Smoking and alcohol consumption during the month before the index pregnancy and since pregnancy started were collected by standardized questionnaires. Depression in early pregnancy was assessed by physician diagnosis or antidepressant use based on universal screening using the Patient Health Questionnaire-9 at the first prenatal visit at KPNC (38).

Covariates

Sociodemographic and obstetric covariates were obtained from structured study questionnaires: age at childbirth (18–24, 25–29, 30–34, ≥35 y), self-reported race or ethnicity (white, Hispanic, African American, Asian/Pacific Islander, other), education (high school or less, some college, college graduate or above), marital status (married/living with partner or not), employment status (full-time, part-time, not employed/missing), nulliparity (yes, no), use of prenatal vitamins before and during pregnancy (yes, no), and infertility treatment (i.e., in vitro fertilization, artificial insemination, and gamete intrafallopian transfer) for the index pregnancy (yes, no). Of note, women were asked to identify themselves as white, black or African American, Hispanic, Asian, Hawaiian/Pacific Islander, American Indian/Alaskan Native, or other groups. Given the small percentage (3.5%) of participants in groups other than white, Hispanic, African American, and Asian/Pacific Islander, we combined them into a multiracial/other/unknown category. Additional covariates were defined using both study questionnaires and EHR data: pre-existing hypertension as ascertained by physician diagnosis and/or antihypertensive medication use (yes, no) and history of PTB (yes, no). A covariate was included in the final model if the coefficient of the exposure of interest changed by ≥10% (39).

Statistical analysis

To examine the associations between individual modifiable prenatal factors and risk of PTB, we first calculated RRs and 95% CIs of PTB associated with each potentially modifiable prenatal factor [i.e., prepregnancy BMI categories (<18.5, underweight; 18.5–24.9, normal weight; 25.0–29.9, overweight; ≥30.0, obesity), AHEI-P score (quartiles), moderate-to-vigorous physical activity (quartiles), PSS score (quartiles), depression (yes, no), smoking before/during pregnancy (yes, no), and alcohol consumption before/during pregnancy (yes, no)] using multivariable Poisson regression models with robust SEs. We adjusted for covariates including age at childbirth, race or ethnicity, education, household income, parity, pre-existing hypertension, and history of PTB, based on the aforementioned covariate selection method (39).

Based on categorical low-risk factors with significant and independent associations with risk of PTB identified from the aforementioned multivariable model as well as the magnitude of individual associations, we further defined 3 binary low-risk factors for simplicity and increased statistical efficiency: healthy prepregnancy BMI of 18.5–24.9, AHEI-P score in the upper quartile (≥67.6 out of 130), and PSS score in the lower 3 quartiles (<17 out of 40), with participants receiving 1 for the presence of a low-risk factor and 0 otherwise. Of note, we parameterized these factors as low-risk instead of high-risk factors in order to facilitate easier interpretation of a healthy lifestyle. We calculated RRs (95% CIs) of PTB risk with each binary low-risk factor, adjusting for the aforementioned covariates and other potentially modifiable risk factors with nonsignificant independent associations with PTB (i.e., physical activity, depression, smoking, and alcohol use). Further, we examined the risk of PTB pertaining to the increasing number of low-risk modifiable prenatal factors (1–3 compared with none) and presence of ≥1 low-risk modifiable prenatal factors (any compared with none), respectively. To reduce potential bias due to missing data on covariates and exposures (ranging from 0.2% in education to 1.0% in smoking during pregnancy), we used multiple imputation based on all other covariates, exposures of interest, and PTB status to create 10 complete data sets, and combined the results on each complete data set using Rubin's rule (40).

We also conducted a priori stratified analyses by PTB clinical subtype (spontaneous and medically indicated) and gestational age at delivery (early: 22–31; moderate: 32–33; or late PTB: 34–36 weeks of gestation). To assess potential effect modification by race or ethnicity, we added a multiplicative interaction term for the presence of ≥1 (any compared with none) low-risk modifiable prenatal factors and race or ethnicity in the multivariable model; we combined women with 1–3 low-risk factors as any to increase the statistical power of the stratified analyses. *P*-for-interaction was obtained by the likelihood ratio test.

To test the robustness of our findings, we in addition adjusted for EHR-abstracted pregnancy complications (i.e., gestational diabetes and hypertensive complications in pregnancy) and gestational weight gain (GWG) of the index pregnancy in multivariable models to assess potential residual confounding, despite the potential overadjustment given the plausibility of pregnancy complications and GWG being on the causal pathway between low-risk prenatal factors of interest and PTB. Given that history of PTB is one of the most important risk factors for PTB (41), we conducted a sensitivity analysis restricted to women with no history of PTB ($n = 2353$). We also performed a sensitivity analysis restricted to women with no gestational diabetes or hypertensive complications in pregnancy ($n = 2009$). All analyses were conducted using SAS version 9.4 (SAS Institute).

Results

Among 2449 women in the PETALS cohort, 160 (6.5%) delivered preterm. Women who delivered preterm compared with at term were more likely to be older; self-identify as African American or Asian/Pacific Islander; have obesity before

TABLE 1 Participants' characteristics before conception and ≤13 weeks of gestation among women with term births and PTBs in the Pregnancy Environment and Lifestyle Study cohort, 2013–2017[1]

	All ($n = 2449$)	Term birth ($n = 2289$)	PTB ($n = 160$)	P value[2]
Age at childbirth, y				0.013
18–24	381 (15.6)	362 (15.8)	19 (11.9)	
25–29	656 (26.8)	624 (27.3)	32 (20.0)	
30–34	879 (35.9)	819 (35.8)	60 (37.5)	
≥35	533 (21.8)	484 (21.1)	49 (30.6)	
Race or ethnicity				<0.001
White	548 (22.4)	519 (22.7)	29 (18.1)	
Hispanic	1006 (41.1)	943 (41.2)	63 (39.4)	
African American	226 (9.2)	204 (8.9)	22 (13.8)	
Asian/Pacific Islander	584 (23.8)	542 (23.7)	42 (26.3)	
Other	85 (3.5)	81 (3.5)	4 (2.6)	
Education				0.65
High school or less	331 (13.5)	307 (13.4)	24 (15.0)	
Some college	936 (38.2)	881 (38.5)	55 (34.4)	
College graduate or above	1175 (48.0)	1098 (48.0)	77 (48.1)	
Household income, annual, $				0.25
<50,000	795 (32.5)	740 (32.3)	55 (34.4)	
50,000–99,999	782 (31.9)	728 (31.8)	54 (33.8)	
100,000–149,999	443 (18.1)	424 (18.5)	19 (11.9)	
≥150,000	393 (17.5)	363 (15.9)	27 (16.9)	
Married/living with their partner	2063 (84.2)	1933 (84.4)	130 (81.3)	0.28
Employment status				0.40
Full-time	1576 (64.4)	1471 (64.3)	105 (65.6)	
Part-time	432 (17.6)	400 (17.5)	32 (20.0)	
Not employed/missing	441 (18.0)	418 (18.3)	23 (14.4)	
Nulliparity	1096 (44.8)	1029 (45.0)	67 (41.9)	0.45
Pre-existing hypertension	105 (4.3)	83 (3.6)	22 (13.8)	<0.001
History of PTB	96 (3.9)	74 (3.2)	22 (13.8)	<0.001
Prepregnancy BMI, kg/m^2				0.002
<18.5	63 (2.6)	60 (2.6)	3 (1.9)	
18.5–24.9	995 (40.6)	949 (41.5)	46 (28.8)	
25.0–29.9	697 (28.5)	650 (28.4)	47 (29.4)	
≥30.0	694 (28.3)	630 (27.5)	64 (40.0)	
Total daily energy intake, kcal	1577.7 ± 701.1	1571.5 ± 692.5	1666.4 ± 812.2	0.09
AHEI-P during the last 3 mo	53.7 ± 10.2	59.8 ± 9.9	57.9 ± 9.8	0.014
PSS score during the last month	12.4 ± 6.4	12.3 ± 6.4	14.0 ± 6.3	0.001
Physical activity met recommendations (≥150 min/wk) during the last 2 mo	365 (14.9)	344 (15.0)	21 (13.1)	0.51
Smoking 1 mo before pregnancy	131 (5.3)	119 (5.2)	12 (7.5)	0.21
Smoking since pregnancy	10 (0.4)	9 (0.4)	1 (0.6)	0.65
Alcohol consumption 3 mo before pregnancy	1247 (50.9)	1170 (51.1)	77 (48.1)	0.56
Alcohol consumption since pregnancy	370 (15.1)	341 (14.9)	29 (18.1)	0.25
Prenatal vitamins use before and during pregnancy	2350 (96.0)	2196 (95.9)	154 (96.3)	0.85
Infertility treatment[3]	50 (2.0)	43 (1.9)	7 (4.4)	0.03
Depression in early pregnancy	268 (10.9)	242 (10.6)	26 (16.3)	0.02
Gestational age at delivery, wk	38.8 ± 1.9	39.2 ± 1.1	33.8 ± 3.1	<0.001
Infant male sex	1253 (51.2)	1172 (51.2)	81 (50.6)	0.95
Infant birth weight, g	3345.0 ± 527.4	3411.6 ± 442.9	2367.5 ± 679.3	<0.001

[1] Values are mean ± SD or n (%) unless indicated otherwise. AHEI-P, Alternate Healthy Eating Index for Pregnancy; PSS, Perceived Stress Scale; PTB, preterm birth.

[2] Obtained by Student's t test for continuous variables or Pearson's χ^2 test for categorical variables.

[3] Included in vitro fertilization, artificial insemination, and gamete intrafallopian transfer.

pregnancy (i.e., BMI ≥ 30.0), pre-existing hypertension, a history of PTB, a lower AHEI-P score, a higher PSS score, and depression; and to have received infertility treatment (all $P < 0.05$) (**Table 1**). Infant's birth weight was lower among those born preterm than among their term counterparts ($P < 0.001$).

Table 2 presents crude and adjusted RRs (95% CIs) of PTB across levels of individual modifiable prenatal risk factors. The risk of PTB increased across prepregnancy BMI categories (P-trend = 0.006) and quartiles of stress levels (P-trend = 0.022) and decreased across quartiles of AHEI-P (P-trend = 0.037), after adjusting for age at childbirth, race or ethnicity, education, household income, parity, pre-existing hypertension, history of PTB, and other potentially modifiable prenatal factors presented in the table. Specifically, obesity compared with normal weight

TABLE 2 Crude and adjusted RR (95% CI) of PTB in association with modifiable prenatal factors among 2449 women from the Pregnancy Environment and Lifestyle Study cohort, 2013–2017[1]

	Women, *n*	PTB, *n*	Crude	Adjusted[2]
Prepregnancy BMI, kg/m^2				
<18.5 (underweight)	63 (2.6)	3 (1.9)	1.09 (0.33, 3.65)	1.13 (0.33, 3.86)
18.5–24.9 (normal weight)	995 (40.6)	46 (28.8)	1 (reference)	1 (reference)
25.0–29.9 (overweight)	697 (28.5)	47 (29.4)	1.41 (0.92, 2.18)	1.49 (0.95, 2.35)
≥30.0 (obese)	694 (28.3)	64 (40.0)	1.91 (1.27, 2.88)	1.93 (1.22, 3.05)
P-trend			<0.001	0.006
AHEI-P score				
Q1 (25.4–51.4)	579 (23.6)	46 (28.8)	1 (reference)	1 (reference)
Q2 (51.5–58.7)	624 (25.5)	38 (23.8)	0.70 (0.44, 1.12)	0.68 (0.42, 1.12)
Q3 (58.8–67.5)	619 (25.3)	40 (25.0)	0.64 (0.40, 1.02)	0.61 (0.38, 1.00)
Q4 (67.6–110.6)	627 (25.6)	36 (22.5)	0.50 (0.29, 0.85)	0.50 (0.28, 0.89)
P-trend			0.023	0.037
MVPA, MET-h/wk				
Q1 (0–2.8)	612 (25.0)	39 (24.4)	1 (reference)	1 (reference)
Q2 (2.9–5.7)	612 (25.0)	39 (24.4)	0.98 (0.61, 1.57)	1.05 (0.64, 1.74)
Q3 (5.8–10.8)	613 (25.0)	45 (28.1)	1.16 (0.73, 1.83)	1.27 (0.78, 2.06)
Q4 (10.9–58.6)	612 (25.0)	37 (23.1)	0.99 (0.61, 1.60)	1.15 (0.69, 1.92)
P-trend			0.802	0.570
Perceived Stress Scale score				
Q1 (0–7)	603 (24.6)	33 (20.6)	1 (reference)	1 (reference)
Q2 (8–11)	549 (22.4)	28 (17.5)	0.91 (0.53, 1.54)	0.88 (0.51, 1.52)
Q3 (12–16)	674 (27.5)	42 (26.3)	1.20 (0.74, 1.95)	1.08 (0.65, 1.79)
Q4 (17–35)	623 (25.4)	57 (35.6)	1.73 (1.07, 2.80)	1.68 (1.02, 2.76)
P-trend			0.009	0.022
Perinatal depression				
No	2200 (89.1)	134 (83.7)	1 (reference)	1 (reference)
Yes	268 (10.9)	26 (16.3)	1.31 (0.82, 2.10)	1.27 (0.78, 2.07)
Smoking before or during early pregnancy				
No	2318 (94.7)	148 (92.5)	1 (reference)	1 (reference)
Yes	131 (5.4)	12 (7.5)	1.00 (0.51, 1.96)	1.01 (0.50, 2.05)
Alcohol consumption before or during early pregnancy				
No	1139 (46.5)	77 (48.1)	1 (reference)	1 (reference)
Yes	1310 (53.5)	83 (51.9)	0.93 (0.67, 1.30)	1.00 (0.70, 1.43)

[1]AHEI-P, Alternate Healthy Eating Index for Pregnancy; MET, metabolic equivalent of task; MVPA, moderate to vigorous physical activity; PTB, preterm birth; Q, quartile.

[2]Adjusted for age at childbirth, race or ethnicity, education, household income, parity, pre-existing hypertension, history of PTB, and all other variables included in the table.

was associated with a 1.93-fold (95% CI: 1.22, 3.05) higher risk of PTB. Overweight (RR: 1.49; 95% CI: 0.95, 2.35) and underweight (RR: 1.13; 95% CI: 0.33, 3.86) compared with normal weight exhibited a higher but not statistically significant risk of PTB. Perceived stress level in the highest compared with the lowest quartile was associated with a 1.68-fold (95% CI: 1.02, 2.76) higher risk of PTB, whereas high-quality diet in the highest compared with the lowest quartile was associated with a 50% (RR: 0.50; 95% CI: 0.28, 0.89) lower risk of PTB. PTB risk did not vary across quartiles of physical activity or by perinatal depression, smoking, and alcohol consumption status, after adjusting for covariates.

For simplicity and increased statistical efficiency, we further derived 3 binary low-risk factors: healthy prepregnancy BMI of 18.5–24.9, AHEI-P score in the upper quartile (≥67.6 out of 130), and PSS score in the lower 3 quartiles (<17 out of 40). Women with a healthy prepregnancy weight, high-quality diet, or low-to-moderate stress, compared with their counterparts without these criteria, had a 42% (RR: 0.58; 95% CI: 0.39, 0.86), 32% (RR: 0.68; 95% CI: 0.39, 0.99), and 40% (RR: 0.60; 95% CI: 0.41, 0.88) lower risk of PTB, respectively (**Table 3**). Women with 1, 2, or 3 low-risk factors compared with none had a 38% (RR: 0.72; 95% CI: 0.45, 1.16), 51% (RR: 0.49; 95% CI: 0.29, 0.84), or 70% (RR: 0.30; 95% CI: 0.13, 0.70) lower risk of PTB, respectively. Further, women with ≥1 of these low-risk factors compared with none had a 39% (RR: 0.61; 95% CI: 0.39, 0.97) lower risk of PTB. Results remained robust and similar in sensitivity analyses with further adjustment for pregnancy complications (gestational diabetes and hypertensive complications in pregnancy) and GWG. In sensitivity analyses restricted to women with no previous history of PTB or women without such pregnancy complications, the associations between increasing number of low-risk modifiable factors and lower risk of PTB were similar to those observed in the entire cohort (**Supplemental Figure 2**).

In stratified analyses by clinical phenotypes of PTB, associations between the presence of ≥1 low-risk factor compared with none and risk of PTB were more pronounced for medically indicated (RR: 0.45; 95% CI: 0.23, 0.85) than for spontaneous PTB (RR: 0.82; 95% CI: 0.44, 1.54) (**Figure 1**), after adjusting

TABLE 3 Crude and adjusted RR (95% CI) of PTB in association with individual and number of low-risk modifiable prenatal factors among 2449 women from the Pregnancy Environment and Lifestyle Study cohort, 2013–2017[1]

	Women, *n* (%)	PTB, *n* (%)	Crude	Adjusted[2]
Individual low-risk modifiable prenatal factors[3]				
Healthy weight (prepregnancy BMI 18.5–24.9 kg/m^2)	995 (40.6)	46 (28.8)	0.59 (0.42, 0.85)	0.58 (0.39, 0.86)
High-quality diet (AHEI-P score ≥ 75th percentile)	627 (25.6)	36 (22.5)	0.69 (0.47, 1.01)	0.68 (0.39, 0.99)
Low-to-moderate stress (PSS score < 75th percentile)	1826 (74.6)	103 (64.4)	0.61 (0.43, 0.86)	0.60 (0.41, 0.88)
Number of low-risk modifiable prenatal factors[3]				
0	306 (12.5)	29 (18.1)	1 (reference)	1 (reference)
1	1067 (43.6)	77 (48.1)	0.72 (0.46, 1.13)	0.72 (0.45, 1.16)
2	838 (34.2)	46 (28.8)	0.51 (0.31, 0.83)	0.49 (0.29, 0.84)
3	238 (9.7)	8 (5.0)	0.28 (0.12, 0.63)	0.30 (0.13, 0.70)
P-trend			<0.001	<0.001
Presence of ≥1 low-risk modifiable prenatal factors[3]				
No	306 (12.5)	29 (18.1)	1 (reference)	1 (reference)
Yes	2143 (87.5)	131 (81.9)	0.59 (0.38, 0.90)	0.61 (0.39, 0.97)

[1] AHEI-P, Alternate Healthy Eating Index for Pregnancy; PSS, Perceived Stress Scale; PTB, preterm birth.

[2] Adjusted for age at childbirth, race or ethnicity, education, household income, parity, pre-existing hypertension, history of PTB, perinatal depression, smoking before or during pregnancy, alcohol consumption before or during pregnancy, and all low-risk prenatal factors listed in the table.

[3] Including healthy weight (prepregnancy BMI 18.5–24.9 kg/m^2), high-quality diet (AHEI-P score ≥ 75th percentile, 67.6), and low-to-moderate stress (PSS score < 75th percentile, 17.0).

for covariates. Similarly, associations were more pronounced for late (RR: 0.57; 95% CI: 0.33, 0.98) than for early (RR: 1.08; 95% CI: 0.34, 3.45) or moderate PTB (RR: 0.48; 95% CI: 0.15, 1.50), although the 95% CIs for the latter 2 overlapped those for late PTB.

The association of having ≥1 low-risk modifiable factor with risk of PTB varied by race or ethnicity (*P*-for-interaction = 0.035) (**Supplemental Figure 3**), but with largely overlapping 95% CIs. Specifically, black women with ≥1 low-risk factor compared with none had a 69% (RR: 0.31; 95% CI: 0.10, 0.93) lower risk of PTB, with a similar magnitude of 63% (RR: 0.37; 95% CI: 0.12, 1.15) among white women, whereas their Hispanic and Asian/Pacific Islander counterparts had a 13% (RR: 0.87; 95% CI: 0.43, 1.75) and 49% (RR: 0.51; 95% CI: 0.16, 1.63) nonsignificantly lower risk, respectively.

Discussion

In this contemporary, racially/ethnically diverse prospective cohort of pregnant women, an overall healthy preconceptional and early-pregnancy lifestyle with combinations of low-risk modifiable factors (i.e., healthy prepregnancy weight, high-quality diet in early pregnancy, and low-to-moderate stress in early pregnancy) was associated with a substantially lower risk of PTB. Women with all 3 low-risk prenatal factors had a 70% lower risk of PTB, independently of other risk factors for PTB. The significant associations of having ≥1 low-risk factor with a lower risk of PTB varied by PTB clinical phenotypes, being more pronounced for medically indicated than for spontaneous PTB.

Multiple maternal characteristics have been individually linked to PTB risk, including genetic, medical, sociodemographic, and behavioral factors (11). The rising trend of PTB prevalence in the United States since 2014 is indicative of the pivotal role of modifiable factors (42). Because the preconception and perinatal periods are a unique and optimal window to promote healthy lifestyle behaviors, primary prevention strategies focusing on potentially modifiable preconceptional and early-pregnancy factors hold promise. Yet, no study to our knowledge has examined the joint associations of multiple modifiable prenatal factors with the risk of PTB. Despite the lack of data on combinations of modifiable prenatal factors in relation to PTB risk, our findings are in line with some, but not all, studies focusing on individual risk factors. Prudent dietary patterns rich in fruits, vegetables, and seafood and low in processed meat and refined grains were associated with a lower risk of PTB among various populations (17), whereas a Mediterranean diet was not associated with PTB in a Norwegian study (43). Notably, empirically data-driven approaches to characterizing dietary patterns may contribute to the inconsistency in findings due to the limited comparability across studies. In this regard, data on a priori diet quality indexes based on national recommendations (e.g., the AHEI-P as used in our study) in relation to PTB risk are warranted, but still scant. Maternal BMI, another indicator of nutritional status, showed positive dose–response associations with risk of PTB in Sweden (13) and Finland (14) but inverse associations with spontaneous PTB among US populations (44, 45). Further, some data linked maternal psychosocial stress to PTB risk (19, 46), whereas others did not (47). In contrast to previous data linking smoking and heavy but not light to moderate alcohol drinking during pregnancy to risk of PTB (48–50), we did not observe similar associations, which could be partially due to the low rates of self-reported smoking (0.4%) and alcohol consumption (15.1%) during pregnancy among our study population. The inconsistent findings may be attributable to the different populations, heterogeneous PTB phenotypes, use of population registries as opposed to cohort data, varied residual cofounding, and the inability to account for potentially synergistic or antagonistic effects of individual risk factors.

Importantly, our study extended the literature beyond the role of individual risk factors to that of an overall healthy lifestyle consisting of multiple preconceptional and early-pregnancy low-risk factors in relation to PTB risk. This may be an important alternative approach, particularly given that multiple prenatal

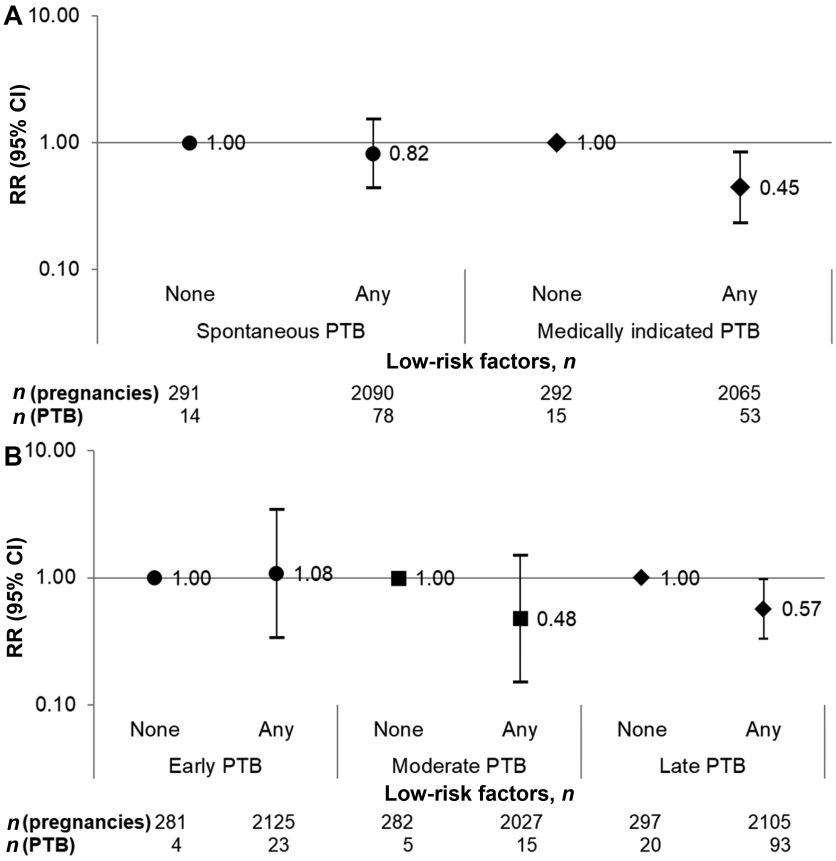

FIGURE 1 Multivariable RR of PTB in association with the presence of ≥1 low-risk modifiable prenatal factor by clinical subtype (A) and gestational weeks (B) of PTB, the Pregnancy Environment and Lifestyle Study cohort, 2013–2017. Early PTB: 22–31 weeks of gestation; moderate PTB: 32–33 weeks of gestation; late PTB: 34–36 weeks of gestation. Low-risk modifiable prenatal factors include healthy weight (prepregnancy BMI 18.5–24.9 kg/m^2), high-quality diet (Alternate Healthy Eating Index-Pregnancy score ≥ 75th percentile), and low-to-moderate stress (Perceived Stress Scale score < 75th percentile). Risk estimates were plotted on a logarithmic scale and adjusted for maternal age, race or ethnicity, education, household income, parity, pre-existing hypertension, history of PTB, perinatal depression, moderate to vigorous physical activity during pregnancy, smoking before or during pregnancy, and alcohol consumption before or during pregnancy. PTB, preterm birth.

factors are interconnected and dissecting the impact of individual components can be difficult.

Notably, 9.7% of women in our cohort had all 3 low-risk modifiable prenatal factors present (i.e., healthy weight, high-quality diet, and low-to-moderate stress). This constellation of low-risk factors was associated with a statistically significant 70% lower risk of PTB than for women without any of these factors. Women with this constellation of low-risk factors may require less monitoring for PTB as demonstrated in the WHO antenatal care randomized trial (51).

Mechanisms whereby an overall healthy prenatal lifestyle consisting of multiple prenatal factors (i.e., healthy weight, high-quality diet, and low-to-moderate stress) lowers the risk of PTB may have shared pathways, including neuroendocrine- and inflammation-mediated processes that have been shown to be related to PTB (11). Obesity may upregulate inflammation by stimulating production of adipokines and proinflammatory cytokines (52). Multiple dietary factors could influence pathways to PTB through immunomodulatory and anti-inflammatory effects via n–3 PUFAs (53), antihypertensive effects via calcium (54), and a supportive role in fetoplacental unit and hemodynamic changes via iron (55). In addition, dietary factors including antioxidant-rich foods such as vegetables and fruits may suppress local and systematic inflammation via the gut microbiome (56), whereas saturated fat may perturb the hypothalamic–pituitary–adrenal axis, which in turn increases production of glucocorticosteroids and subsequent inflammation (57). In addition, women exposed to stressful conditions have increased concentrations of corticotropin-releasing hormones which interact with prostaglandins and oxytocin, 2 major uterotonins that act on myometrium during labor (58).

We observed more pronounced associations of having ≥1 prenatal low-risk factor with medically indicated than with spontaneous PTB, suggesting a greater impact of an overall healthy prenatal lifestyle on medically indicated PTB. It is plausible that pregnancy complications underlying the medical indications for PTB may be driving the more pronounced association. Future formal investigations into the potential mediation effect of pregnancy complications in the association between healthy prenatal lifestyle and risk of PTB, especially medically indicated PTB, may be warranted. The association of having ≥1 prenatal low-risk factor was more pronounced with late than with early or moderate PTB, which, however, could be partially attributed to the larger sample size and greater statistical power of

the late PTB subgroup, as evidenced by the wide 95% CIs of early or moderate PTB. In addition, we found that the associations of preconceptional and early-pregnancy low-risk modifiable factors with lower risk of PTB varied statistically by self-identified race or ethnicity. However, we did not observe meaningful racial or ethnic differences in the associations between these lifestyle factors and PTB risk, given the largely overlapping 95% CIs, which could be partially attributed to the limited statistical power in our stratified analyses. Future larger-scale studies among diverse cohorts of women are warranted.

The major strengths of our study include its prospective design, a diverse population, the use of early ultrasound-confirmed obstetric estimates of gestational age to ensure greater accuracy as recommended by the American College of Obstetricians and Gynecologists, and the detailed information on a wide range of risk factors for PTB using validated questionnaires and robust clinical data. Besides the adjustment for confounders, universal access to prenatal care for all pregnant women in the cohort is an additional strength because it further limits the possibility of residual confounding and increases internal validity. Further, with detailed clinical data abstracted from the EHR, we were able to study PTB by clinical phenotypes.

Several potential limitations of the study merit note. Among women carrying singleton pregnancies, the prevalence of PTB was 6.5% in our study (2013–2017), slightly lower than that (6.7%–7.1%) in California in 2013–2017 (59), which could be partially due to the exclusion of women with major pre-existing diseases in our study. Maternal dietary intakes were self-reported using the FFQ in early pregnancy, leading to potential recall bias and exposure misclassification. However, the FFQ has been validated against three 4-d diet records and demonstrated its applicability to analyses on food-group and nutrient levels (60, 61). We did not have data on maternal diet in mid-to-late pregnancy; however, diet quality in early pregnancy may be a harbinger of that in later pregnancy and previous studies suggest that dietary patterns change little across pregnancy (62, 63). Further, despite the potential overadjustment bias, we in addition adjusted for GWG, an indicator of the intrauterine nutritional environment across gestation; reassuringly, results remained robust. Finally, our findings were observational and may not be causal. Nonetheless, given the current paucity of data on combinations of modifiable risk factors and PTB risk, carefully conducted observational studies are a critical step to inform the future development, testing, and potential implementation of multicomponent preventive strategies for PTB.

In conclusion, our study found a substantially lower risk of PTB among women with an overall healthy prenatal lifestyle characterized by a healthy prepregnancy weight, high-quality diet in early pregnancy, and low-to-moderate stress in early pregnancy. Our findings suggest the potential importance of providing multicomponent interventions as primary prevention strategies that target weight management, dietary quality, and psychological health during preconception and early pregnancy to mitigate the risk of PTB in clinical settings. For women without adequate access to prenatal clinical care, our findings reinforce the importance of appropriate referrals to resources such as the Special Supplemental Nutrition Program for Women, Infants, and Children to promote healthy eating and weight management and social work services to support mental health and stress management.

The authors' responsibilities were as follows—YZ: conceived the study concept, analyzed the data, and drafted the manuscript; AF: designed and oversaw the study; JF: contributed to data analysis; AF, MMH, SDB, SEB, CPQ, and JF: revised the manuscript; MMH, SDB, SEB, CPQ, and JF: contributed to data interpretation; YZ and AF: are the guarantors of this work and, as such, had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis; and all authors: contributed to the interpretation of the results and revision of the manuscript for important intellectual content and read and approved the final manuscript. The authors report no conflicts of interest.

Data availability

Data described in the article, code book, and analytic code will not be made available because of the electronic health record data and confidential nature of the data collected.

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